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09/990,705	11/21/2001	Judith K. Gwathmey	JGT-004	3899

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BOSTON, MA 02109

EXAMINER

AFREMOVA, VERA

ART UNIT

PAPER NUMBER

1651

DATE MAILED: 06/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/990,705

Applicant(s)

Gwathmey et al.

Examiner

Vera Afremova

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Mar 18, 2003
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above, claim(s) 14-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

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DETAILED ACTION

Election/Restriction

Applicants' election without traverse of the Group I invention (claims 1-13) in Paper No. 9 filed 3/18/2003 is acknowledged. Claims 14-26 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 1-13 are under examination in the instant office action.

Claim Objections

Claim 1, 2, 12 and 13 are objected to because of the following informalities:

Claims 1, 2, 12 and 13 appear to contain some typing error in the name of the solution "Earl's". Is it Eagle's medium?

Claim 2 recites "acid" twice, for example; see line 4.

Appropriate corrections are required.

Claim Rejections - 35 USC § 112

Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are indefinite with regard to the phrase "decreasing"(claims 1 and 13), "increasing"(claims 1 and 13), "decreases" (claim 6) and "increases" (claim 10) as related to calcium concentrations. It is uncertain what are starting and final concentration and to how many

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various concentrations or solutions the tissue is exposed. Further, it is also unclear as claimed whether the processes are intended as a continuous perfusion or a batch cultivation. It is unclear whether and when the processes are intended as a step-wise batch cultivation. It is unclear what is actually done in the claimed method to provide for "decreasing" and "increasing" calcium concentrations. This concept is also unclear in the light of specification, for example: on page 6, par. 3, the same concentration is disclosed for all solutions but the paragraph bridging pages 6 and 7 discloses the increasing concentrations in all solutions.

Furthermore, it is uncertain what are the differences, if any, between the decreases in calcium amounts in step (b) in the method of claim 1 and in the method of claim 6. It is also uncertain what are the differences, if any, between the increases in calcium amounts in step (d) in the method of claim 1 and in the method of claim 10.

In addition, it is uncertain whether the claimed "Earle's modified salt" component (claims 1, 2, 12 and 13) contains some calcium. For example: ATCC catalogue discloses two Eagle's media with two different calcium concentrations (page 517). Thus, a relationship between calcium concentrations in the Eagle's/Eagle's component and in the other claimed solutions is uncertain as claimed to point out the intended changes in the amounts of calcium through the whole claimed method.

Claims 12 and 13 are indefinite with regard to particular concentrations of various components in the "second solution" because some amounts of them are expressed for one liter, some are expressed for 500 ml, some do not indicate for what volume they are intended (for

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example: ascorbic acid 8.8 mg), some are uncertain to what the volume of what solution they are intended (for example: % v/v).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Kruppenbacher et al. [IDS-C4] taken with the ATCC catalogue [U] and Kang et al. [IDS-C3].

Claims are directed a method of isolating cells comprising step of obtaining a tissue sample from a subject, step of successively exposing the tissue to a first solution with decreasing amounts of CaCl_2 comprising NaCl, HEPES, MgCl_2 , KCl and sugar at pH about 7.4, step of disassociating the tissue with an enzyme solution, step of repeatedly resuspending the disassociated tissue into second solution with increasing amounts of CaCl_2 comprising salts, L-glutamine, sodium bicarbonate, sodium pentothenate, creatine, taurine, ascorbic acid, HEPES, fetal bovine serum, antibiotic, and fatty acid at pH about 7.4 to obtain isolated cells. Some claims are/are further drawn additional step of resuspending the isolated cells. Some claims are further drawn to incubating isolated cells in a mixture of carbon dioxide and air at temperature 37°C. Some claims are further to exposing the tissue to a first solution at 37°C at 4 ml/min for 3

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minutes. Some claims are further drawn to the use of digestive enzyme protease or collagenase in the enzyme solution a method of isolating cells. Some claims are further drawn to particular concentration of the ingredients in the first and in the second solutions. Some claims are further drawn to the use of particular ingredient in the enzyme solution such as NaCl, HEPES, MgCl₂, KCl and glucose at particular concentrations.

Kruppenbacher et al. [IDS-C4] discloses a method of isolating cells or cardiomyocytes wherein the method comprises comprising step of obtaining a heart tissue sample from a subject (page 133, col. 1, lines 14-16); step of successively exposing the tissue to a first solution or buffer with decreasing amounts of CaCl₂ from 25 μ M (page 133, col. 1, line 24) to zero as in water (page 133, col. 1, lines 33-36) wherein the first solution of buffer comprising NaCl, Mg salt, KCl and glucose (page 133, col. 1, lines 20-22); step of disassociating the tissue with an enzyme solution comprising digestive enzymes protease (trypsin) and collagenase (page 133, col. 1, line 25) as well as other components of the first buffer solution including NaCl, HEPES, MgCl₂, KCl and glucose (page 133, col. 1, lines 20-22); step of repeatedly resuspending the disassociated tissue and cells into second solution or buffer with increasing amounts of CaCl₂ such as 0.2/0.2/1.0 mM and finally in M 199 culture medium comprising salts, sodium bicarbonate, creatine, taurine, fetal bovine serum and antibiotic (page 133, col. 2, lines 5-12). The cited reference discloses incubating isolated cells in a mixture of carbon dioxide and air at temperature 37°C (col. 3, line 6). The cited reference discloses step of exposing the tissue to a first solution at 37°C at 4 ml/min for 20 minutes (page 13, col.1, line 26).

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The cited reference by Kruppenbacher et al does not disclose the use of buffer HEPES in the first solution but it clearly teaches the use of a buffer which is a physiologically acceptable buffer and which is reasonably expected to have neutral pH of about 7.4. The periods of the tissue exposure to the first solution in the method of the cited reference appears to be different but the claimed method does not indicate how many steps and how much tissue materials have been used in the method for isolating cells from the tissue.

The cited reference by Kruppenbacher et al. is silent with regard to the M 199 medium ingredients. However, it is known that the medium M 199 comprises ingredients required by the presently claimed method including ascorbic acid and sodium pentothenate, for example: see ATCC catalogue page 522.

The cited reference by Kruppenbacher et al does not disclose the use of fatty acid in the solution or in the culture medium for cardiomyocytes. But the reference by Kang et al. [IDS-C3] teaches the use of fatty acid in the solution/culture medium for cardiomyocytes (see abstract) wherein the solution/medium comprises all other ingredients required by the presently claimed invention including NaCl, HEPES, $MgCl_2$, KCl, glucose as well as calcium (page 9887, col. 1, lines 1-2).

The cited reference by Kruppenbacher et al does not disclose the identical concentrations of nutrients in the solutions/media as required by the claimed method, however, the use of particular amount of nutrients in the cell culture media is reasonably expected to be adjustable with regard to physiological requirements of a particular cell or tissue culture system.

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Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice a method of isolating cells by treating the tissue with decreasing amounts of CaCl_2 and the cells with increasing amounts of CaCl_2 as taught by the reference by Kruppenbacher et al with a reasonable expectation of success in isolating viable and active cells from the tissue as taught by the reference by Kruppenbacher et al. The cited method Kruppenbacher et al. is substantially similar, if not identical, to the presently claimed method as explained above. It is considered to be within the purview of one of skill in the art to adjust intervals of incubation, pH and amounts of nutrients with regard to a particular cell or tissue culture system. One of skill in the art is would have been motivated to do so for the expected benefits in maximizing effects related to cell survival and activity. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

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June 13, 2003.

VERA AFREMOVA

PATENT EXAMINER

A handwritten signature in cursive script, appearing to read "V. Afremova", with a long horizontal flourish extending to the right.